UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation This Document Relates To: *All Cases*	Docket No.: 22-md-3043 (DLC)

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERTS' OPINIONS REGARDING BIOLOGICAL PLAUSIBILITY/MECHANISM

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Plaintiffs have proffered five experts—Drs. Andrea Baccarelli, Robert Cabrera, Eric Hollander, Stan Louie and Brandon Pearson—to address general causation: whether in utero acetaminophen exposure can cause either autism spectrum disorder ("ASD") or attention-deficit/hyperactivity disorder ("ADHD"). As part of their answers to these questions, each expert addresses biological plausibility: "whether the hypothesized causal link [with ASD or ADHD] is credible in light of what is known from science and medicine about the human body and the potentially offending agent." *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at *5 (S.D.N.Y. Sept. 3, 2021) (citation omitted), *aff'd*, No. 22-146, 2023 WL 4837521 (2d Cir. July 28, 2023). Biological plausibility is critical to the general causation question because "a biological explanation without evidence of the mechanism by which it works is merely an unproven hypothesis, a theory." *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007); *Kilpatrick v. Breg, Inc*, No. 08-10052-CIV, 2009 WL 2058384, at *5 (S.D. Fla. June 25, 2009) (excluding expert's causation opinion in part because "none of the articles [on which he relied] explains the mechanism" by which the medication allegedly causes the injury). Biological plausibility is necessary—but not sufficient—to establish general causation.[1]

Rather than identify a plausible mechanism, plaintiffs' experts throw out several hypotheses, hoping one will stick. All of plaintiffs' theories are wildly speculative, and all involve the very sorts of analytical gaps that are prohibited under *Daubert.*

First, plaintiffs' experts ignore that scientists have not determined the physical and

[1] Biological plausibility is just one component of the causal inquiry. The existence of a plausible biological mechanism would not suffice for plaintiffs' experts to reliably opine that prenatal acetaminophen exposure can cause ASD or ADHD absent satisfaction of other Bradford Hill considerations, such as strength of association, consistency and dose response. Defendants' other two *Daubert* motions addressing those and other issues are incorporated herein by reference.

biochemical processes that lead to either ASD or ADHD, meaning that all of their theories are just "scientific guesswork." Without knowing the causal pathway by which either disorder can develop, plaintiffs' experts cannot reliably bridge the gap between the scattered neurobiological changes they purport to identify in rodents and the etiology of ASD or ADHD in humans.

Second, plaintiffs' experts performed results-oriented and unreliable reviews of the literature by cherry-picking isolated findings of neurochemical changes, while ignoring the great weight of contrary evidence. That approach is particularly unreliable in this litigation because many of the studies at issue contain dozens of end points, meaning that an occasional positive result would be expected by chance alone.

Third, review of each individual proposed mechanism makes these and other methodological errors plain. Plaintiffs' experts focus most on their oxidative stress theory. According to this theory, a minor metabolite of acetaminophen known as NAPQI is further metabolized in the fetus by the antioxidant glutathione ("GSH"). Plaintiffs' experts posit that the NAPQI overwhelms the GSH, resulting in excess NAPQI, generating oxidative stress that leads to some type of adverse neurodevelopmental outcome. But both major steps—the creation of oxidative stress in utero and the link between oxidative stress and ASD or ADHD—lack scientific support. In an attempt to plug that hole in the science, plaintiffs' experts cherry-pick isolated findings in the literature, while ignoring contrary results from the same authors, and even from the same studies.

Plaintiffs' experts also speculate that acetaminophen, and a different, and even more minor, metabolite, AM404 can disrupt the endocannabinoid system (a network of chemical signals and cellular receptors in human brains and bodies that regulates key bodily functions) by binding to certain receptors and limiting the reuptake of a chemical called anandamide. This

theory, too, depends on a tenuous chain in which no step has been adequately established.

Plaintiffs' experts further surmise that epigenetic changes—i.e., changes in gene expression—might cause ASD and ADHD. Again, plaintiffs' experts rely on findings that have never been replicated, while ignoring studies to the contrary. In addition, most of the epigenetic changes that they purport to identify do not relate to ASD or ADHD, and none of them have been shown to take place in the human brain.

Some of plaintiffs' experts advance additional speculative theories as well. Dr. Pearson suggests that acetaminophen might affect other neurotransmitter levels, influencing, among other things, serotonergic signaling. Some of plaintiffs' experts also propose that acetaminophen exposure in utero might alter levels of brain-derived neurotrophic factor ("BDNF"), a protein involved in supporting the growth of neurons. Yet another hypothesis they offer is that acetaminophen or its metabolites can be directly toxic to cells, causing cell death. Finally, some plaintiffs' experts posit that acetaminophen can cause unspecified neurodevelopmental issues by interfering with the prostaglandin system. (Prostaglandins are hormone-like substances that affect inflammation and pain.) In advancing these hypotheses, plaintiffs' experts cherry-pick from inconsistent results, usually in rodents, with no reliable evidence that any of these changes—if they do happen—can cause ASD or ADHD.

BACKGROUND

Each of plaintiffs' five experts offers opinions related to biological plausibility.

I. DR. BRANDON PEARSON

The "primary" mechanistic theory offered by plaintiffs' expert toxicologist Dr. Pearson is that acetaminophen is metabolized into NAPQI, which leads to oxidative stress and resulting neurodevelopmental impairment. (Am. Rep. of Brandon Pearson ("Pearson Rep.") at 51, June 21, 2023 (Ex. 8); *see id.* at 51-56.) As explained above, Dr. Pearson and plaintiffs' other experts

opine that acetaminophen exposure can cause NAPQI levels to "exceed[]" "GSH reserves," allowing NAPQI to accumulate and promote oxidative stress. (*Id.* at 52.) This oxidative stress, in turn, is theorized to "result in damage to developing neurons," as well as to decrease maternal and fetal defenses against other future oxidants, resulting in damage to fetal brain development. (*Id.* at 53.)

Dr. Pearson also proposes additional mechanisms. He hypothesizes, for example, that acetaminophen can cause programmed cell death, which he concedes is necessary at ordinary levels, but in his opinion, "can be a highly undesirable outcome during neurodevelopment." (*Id.* at 58-60.) Additionally, he suggests that acetaminophen leads to "dysregulation of the endocannabinoid system," mainly because AM404, an acetaminophen metabolite, inhibits uptake of anandamide by endocannabinoid receptors, leading to greater levels of free anandamide (*id.* at 61-63 (capitalization altered)). Relatedly, he claims that acetaminophen disrupts other neurotransmitters, including those related to "serotonergic signaling," which is supposedly "crucial for normal neurodevelopment." (*Id.* at 64-65.) Dr. Pearson also suggests that acetaminophen has ill-defined "effects on brain-derived neurotrophic factor (BDNF)" (*id.* at 63 (capitalization altered)), and that its inhibition of prostaglandins harms the developing brain because "[p]rostaglandin receptors are present in a variety of locations in the brain" (*id.* at 65-66). Finally, he posits that acetaminophen can cause epigenetic changes (i.e., changes in gene expression without alteration to the underlying DNA sequence), although he largely defers to other experts, and specifically to Dr. Baccarelli, on this issue. (*Id.* at 60-61.)

Rather than attempt to explain how these supposed neurochemical changes actually cause ASD or ADHD, Dr. Pearson generally asserts that the relevant systems are important for neurodevelopment and implies that their disruption must cause some problem (*see, e.g.*, *id.* at 53

("[o]xidative stress" can "leave a developing brain vulnerable")), or relies on the fact that disruptions to certain systems co-occur with ASD or ADHD (*see, e.g.*, *id.* at 62 ("Endocannabinoid metabolism has been shown to be disrupted in childhood ADHD."); *id.* at 65 ("alterations in serotonin level[] receptors in autistic people")).

Despite recognizing the need for replication, Dr. Pearson cherry-picks from literature that includes inconsistent (and in some cases irreconcilable) results to claim an association between acetaminophen use and a series of biomarkers. In his rebuttal report, Dr. Pearson attempts to justify such cherry-picking and his reliance on non-replicated studies by rejecting a "rigid view of replication" because "[i]t is not to be expected that every study author . . . finds exactly the same thing." (Rebuttal Rep. of Brandon Pearson at 5, July 28, 2023 (Ex. 18); *see also* Dep. of Brandon Pearson ("Pearson Dep.") 144:13-25, Aug. 11, 2023 (Ex. 17) (evaluating "consistency" of the evidence was "not [his] goal").) Indeed, he went so far as to testify at his deposition that studies could be deemed consistent if they had opposite results—one showing an increase in levels of a neurochemical for instance, and the other showing a decrease. (*See* Pearson Dep. 63:7-11, 76:8-11, 275:4-276:18.) Dr. Pearson did concede at his deposition that the studies purporting to show an association between ASD or ADHD and certain biomarkers could not distinguish between circumstances that may have caused a disorder and those that result from it, even though he relies heavily on such studies to link neurochemical changes to clinical outcomes. (*See id.* 254:13-255:11.)

II. DR. STAN LOUIE

Dr. Louie, a pharmacist and pharmacologist, proposes two primary biological mechanisms. The first and most prominent relates to excess NAPQI and oxidative stress, as well as an associated inflammatory response. (*See* Am. Rep. of Stan Louie ("Louie Rep.") ¶¶ 104-36, 155-67, June 21, 2023 (Ex. 9).) That theory proceeds on much the same lines as Dr. Pearson's.

(*See id.* ¶¶ 110, 167 (positing that depletion of GSH can "reduce the ability to manage and suppress fetal oxidative stress," which "may . . . increase risk of neurodevelopmental disorder[s]").) Alternatively, Dr. Louie proposes that acetaminophen can cause epigenetic changes by leading to DNA methylation (in which a methyl group is added to the DNA molecule) which then "lead[s] to neurodevelopmental disorders." (*See id.* ¶ 172.) Dr. Louie does not explain how the methyl group would have any clinical significance, let alone how it would lead to ASD or ADHD.

In addition to his two primary theories, Dr. Louie references a few others—that acetaminophen can impact BDNF levels (*see id.* ¶ 153) and that it can cause the death of neurons (*see id.* ¶ 154). These are barely formed opinions; Dr. Louie simply recites an animal study with no attempt to link the purported neurochemical changes he identifies to ASD or ADHD, or even to the brain more generally. (*See, e.g.*, *id.* ¶ 64 (relying on liver study and ipse dixit assertion about similarity between brain and liver).)

At his deposition, Dr. Louie could not identify "the biological mechanisms that lead to autism spectrum disorder" (Dep. of Stan Louie ("Louie Dep.") 50:15-23, Aug. 7, 2023 (Ex. 10); *see id.* 44:14-23, 45:19-46:21, 53:6-20), and he acknowledged that oxidative stress could be the result of ASD, as opposed to its cause (*id.* 266:24-267:22).

III. DR. ROBERT CABRERA

Dr. Cabrera, a biologist who specializes in teratology, claims to have performed a systematic review of the literature, from which he determined, among other things, that there exists a "causal-plausible interaction between" acetaminophen and generalized "neurodevelopmental adverse outcomes." (Am. Rep. of Robert Cabrera ("Cabrera Rep.") at 192, June 22, 2023 (Ex. 6).) Dr. Cabrera's report mentions a series of proposed pathways, including the theory that acetaminophen "disrupt[s] . . . prostaglandins" and "impacts . . . serotonergic

pathways." (*Id.* at 52-53.) At his deposition, however, Dr. Cabrera backtracked, testifying that those discussions were intended only for "background" and that his ultimate biomechanical and causation opinions are limited to theories related to oxidative stress and endocannabinoid pathways. (Dep. of Robert Cabrera ("Cabrera Dep.") 325:2-326:15, Aug. 2, 2023 (Ex. 7).) Dr. Cabrera's opinions on these issues are similar to those offered by Drs. Pearson and Louie. With respect to oxidative stress, he opines that acetaminophen exposure leads to "the depletion of GSH," and that "[w]hen GSH is depleted, free radicals—including NAPQI . . .—are unimpeded." (Cabrera Rep. at 40-41.) Dr. Cabrera theorizes that this ultimately leads to "oxidative stress-induced damage [that] can disrupt normal neural development," but he does not connect that supposed "disruption" to ADHD or ASD. (*Id.* at 45.) With respect to endocannabinoids, Dr. Cabrera theorizes that AM404 "increases brain endocannabinoid levels by decreasing the reuptake of anandamide." (*Id.* at 49.)

Dr. Cabrera frames much of his review around an Adverse Outcome Pathway ("AOP") that deals with ***learning and memory***, not with ASD or ADHD. (*See id.* at 35.) AOPs assess how adverse outcomes may arise, and many have been published by the Organisation for International Co-operation and Development ("OECD"), an intergovernmental organization. As Dr. Cabrera was forced to admit at his deposition, however, the AOP around which he framed his opinions not only fails to address ASD or ADHD, but was specifically edited to delete references to ASD because conclusions as to that disorder were unsupported. (*See* Cabrera Dep. 317:23-319:18.)

As part of his analysis, Dr. Cabrera evaluates mechanistic studies, most of them performed on rodents, though some were performed on humans or in vitro. Many of these studies, such as those that assessed sexual behavior, have no conceivable relevance to ASD or

ADHD. Dr. Cabrera also often relies on generalities that do not link any findings with any developmental disorder—for example, that "oxidative stress-induced damage can disrupt normal neural development" or that "cannabinoid . . . signaling [is] essential for normal tissue and organ development." (Cabrera Rep. at 45, 66.) In addition, like Dr. Pearson, he depends on correlations between certain biomarkers and the disorders, without any understanding of whether the biomarker at issue actually causes the disorder. (*See id.* at 67 ("Patients with ASD have greater markers of oxidative stress.").)

At his deposition, Dr. Cabrera admitted that not all neurotoxicity leads to ASD or ADHD, and that the focus of analysis should be on the two specific disorders of interest. (*See* Cabrera Dep. 180:24-181:10, 188:2-4.) He further acknowledged that he limited his opinions on what causes ASD and ADHD to oxidative stress and endocannabinoid disruption because there were "gaps in the data" with respect to plaintiffs' experts' myriad other theories (*id.* 325:17-326:1).

IV. DR. ERIC HOLLANDER

Dr. Hollander, a psychiatrist, uses the term "transdiagnostic approach" to blur the lines between ASD and ADHD. (Am. Rep. of Eric Hollander ("Hollander Rep.") at 11-12, June 22, 2023 (Ex. 11).) Although Dr. Hollander does separately enumerate the proposed pathophysiology for the two disorders, he offers a single set of mechanisms that he thinks can cause both conditions. The first two hypotheses are closely related: excess NAPQI formation depleting GSH and the resultant oxidative stress. (*See id.* at 76-79.) As with the other experts, Dr. Hollander theorizes that in cases of excessive exposure to acetaminophen, "concentrations of NAPQI exceed the available GSH," causing a "cascade" of effects, including oxidative stress, to which "[t]he developing human brain is highly susceptible." (*Id.* at 77-78.) He also echoes plaintiffs' other experts' suggestions that acetaminophen can cause "endocannabinoid dysfunction" by preventing anandamide reuptake, although, unlike the other experts, he adds that

"[r]epeated exposure . . . sets the [long-term] level of anandamide lower," for reasons left unexplained. (*Id.* at 79-81.) Dr. Hollander also claims that acetaminophen "has been associated with epigenomic alterations" and that such alterations can "result in neurodevelopmental disorders." (*Id.* at 83-85.) In addition, his report suggests that acetaminophen "has been postulated" to disrupt "the signaling of" a prostaglandin pathway and thereby cause neurodevelopmental disorders (*id*. at 79) and that acetaminophen "alters" BDNF, which "is involved in several important neurodevelopmental processes" (*id*. at 82-83). Finally, Dr. Hollander mentions the possibility of endocrine disruption, but stops short of concluding that acetaminophen is an endocrine disruptor, stating only that "evidence is still being developed." (*Id.* at 82.) Despite the number of mechanisms proposed in his report, Dr. Hollander testified that only oxidative stress, endocannabinoid disruption and epigenetic changes constitute "plausible biological mechanisms." (Dep. of Eric Hollander ("Hollander Dep.") 381:25-382:14, Aug. 9, 2023 (Ex. 13).)

V. DR. ANDREA BACCARELLI

Although the overwhelming majority of Dr. Baccarelli's report focuses on epidemiology, he does propose several mechanisms that he thinks "plausib[ly] link[] in utero exposure [to acetaminophen] with altered fetal brain development." (Am. Rep. of Andrea Baccarelli ("Baccarelli Rep.") at 44, June 23, 2023 (Ex. 2).) To a large degree, those mechanisms track the ones presented by other experts, though in even more cursory form. As to the NAPQI theory, for example, his entire explanation is that "[t]he developing brain is highly susceptible to the effects of oxidative stress." (*Id.* at 45; *see also*, *e.g.*, *id.* at 47 (BDNF); *id.* at 48-50 (epigenetics).) In addition, Dr. Baccarelli is the only expert to seriously propose that acetaminophen can cause

ASD and ADHD through endocrine disruption, though he does not develop this theory.[2]

Like plaintiffs' other experts, Dr. Baccarelli offers only generalities to bridge the gap between supposed neurochemical effects and the development of ASD or ADHD. For instance, he asserts that the endocannabinoid system "ha[s] an important role in the developing nervous system" (*id.* at 46) and that "BDNF . . . support[s] the development and function of the nervous system" (*id.* at 47), without tying those supposed relationships to the specific conditions of ASD or ADHD. He also assumes without support that changes observed in individuals who have ASD or ADHD are causes of the condition rather than results of it. (*See, e.g.*, *id.* at 46.)

ARGUMENT

The Second Circuit *Daubert* standard is set forth in Defendants' Motion to Exclude Testimony That Acetaminophen Exposure Can Cause Autism Spectrum Disorder ("ASD *Daubert* Brief") and incorporated herein. Under *Daubert*, a court should consider: "1) whether a theory or technique can be (and has been) tested; 2) whether it has been subjected to peer review or publication; 3) the 'known or potential rate of error' for the expert's technique and whether there are 'standards controlling the technique's operation'; and 4) whether the expert's technique or theory is generally accepted in the relevant scientific community." *Daniels-Feasel*, 2021 WL 4037820, at *4 (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593 (1993)). If an opinion "fail[s] all four" factors, the "court must 'carefully scrutinize,' pause, and take a 'hard look' at the expert's methodology." *Id.* (quoting *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 240 (S.D.N.Y. 2018) ("*Mirena II* (District)"), *aff'd*, 982 F.3d 113 (2d Cir. 2020) ("*Mirena II* (Circuit)")).

[2] Because only Dr. Baccarelli advances this theory and only in passing, defendants do not address it in detail below.

None of those factors is satisfied here. As an initial matter, plaintiffs' experts have not submitted the mechanistic theories they advance in this litigation for peer review or publication, as most of them acknowledged at their depositions. (*See, e.g.*, Hollander Dep. 24:20-25:8 (never published on acetaminophen); Louie Dep. 18:21-19:9 (never published on ASD); Cabrera Dep. 29:2-30:9 (did not even have an opinion on ASD or ADHD and acetaminophen prior to this litigation).) In addition, speculation about potential mechanisms for the development of ASD and ADHD obviously has no known or potential rate of error. And plaintiffs' experts' theories of biological plausibility, and ultimately causation, have certainly not been generally accepted by the mainstream scientific community. *See In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 449 (S.D.N.Y. 2016) ("*Mirena I*") (general acceptance requires more than "some members of the medical and scientific community who agree").) To the contrary, the U.S. Attorney for the Southern District of New York told the Court just a week ago that the FDA has again rejected a "determination of [a] causal[]" relationship. (Dkt. No. 1105 at 2.)

Accordingly, under *Mirena II*, the Court must take a "hard look" at plaintiffs' experts' theories. For the reasons set forth below, plaintiffs' experts' biological plausibility opinions cannot stand up to such a "hard look."

I. PLAINTIFFS' EXPERTS' MECHANISM THEORIES REST ON SEVERAL UNRELIABLE LEAPS OF LOGIC.

The first and most fundamental problem with plaintiffs' experts' opinions is that they do not know the biological pathways by which either ASD or ADHD develops, making it impossible for them to explain how acetaminophen could cause either condition and rendering their opinions entirely speculative.

Experts seeking to opine that an exposure can cause an injury must offer "evidence to carry them all the way down their causal chain." *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp.

2d 398, 426 (S.D.N.Y. 2005) ("*Rezulin II*"); *see, e.g.*, *Mirena II* (District), 341 F. Supp. 3d at 270-71 (excluding theory of biological plausibility that "relie[d] on too many unsupported leaps"); *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1357-58 (S.D. Fla. 2011) (excluding testimony from mechanistic experts because they did not offer support for every step in the causal chain); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 524 F. Supp. 3d 1007, 1041-42 (S.D. Cal. 2021) ("a mechanism expert must support 'every necessary link' in their biological theory with supporting evidence"); *cf. Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002) ("[I]t is critical that an expert's analysis be reliable at every step."). Plaintiffs' experts' opinions here lack reliable evidence at multiple links in the causal chain.

First, plaintiffs have not identified any process or biological pathway through which ASD or ADHD generally develops. Where, as here, the precise pathogenesis of a condition is unknown, an expert seeking to opine that it is biologically plausible that a certain environmental exposure causes the condition must explain the "mechanics of" that condition, including "the threshold issue of . . . how this condition comes about." *Mirena II* (District), 341 F. Supp. 3d at 285 (excluding mechanism expert); *In re Accutane*, 511 F. Supp. 2d at 1295-96 (excluding expert who "developed a biological theory regarding how [drug] might cause [disease]" as "merely plausible, not proven," because "at this point, no one knows the exact biological mechanism by which [disease] occurs"); *see also Hendrix v. Evenflo Co.*, 609 F.3d 1183, 1202 (11th Cir. 2010) (affirming exclusion of expert and noting that with exception of a few chromosomal abnormalities, "medical science simply does not know what causes autism"). Without explaining the underlying formation process of a condition, an expert can offer nothing but a "bare assumption that some such biological pathway must exist." *Mirena II* (District), 341

F. Supp. 3d at 285.

In *Mirena II*, for example, Judge Engelmayer excluded an opinion offered by a plaintiffs' expert who articulated a "mechanism theory" that high concentrations of a synthetic hormone released by a birth control device could cause idiopathic intracranial hypertension ("IIH"). *See* 341 F. Supp. 3d at 284. As the court explained, "[a]lthough the immediate cause of IIH is the excessive buildup of [cerebrospinal fluid], IIH's pathogenesis—the biological mechanism that brings it about—is poorly understood," *id.* at 223, and the expert at issue did not address that "threshold issue of what IIH is and how this condition comes about," *id.* at 285. Because the expert gave "scant attention to the actual pharmacokinetic process" underlying his postulated causal sequence, his methodology "fail[ed]" and his opinions were excluded. *Id.* at 285-86 ("[S]ilences on these points—about the mechanics of IIH, and about the basic operation of the 'mechanism' and 'pathway' that he posits link [drug] to this rare disease . . . are failures of methodology."). The Second Circuit affirmed Judge Engelmayer's holding, commending his "rigorous review" of the proffered expert testimony. *Mirena II* (Circuit), 982 F.3d at 124.

Hendrix applied the same principle in the context of ASD specifically. There, a mother sued a car-seat manufacturer, alleging that as a result of defects in the seat, her infant suffered a traumatic brain injury that caused him to develop autism. *See Hendrix v. Evenflo Co.*, 255 F.R.D. 568, 574-75 (N.D. Fla. 2009). The district court excluded the opinion because "identifying a cause of autism does not appear to be within the realm of current medical science," and "until such time as medical science understands the physiological process by which autism develops and how the process occurs, the law cannot impose liability for autism." *Id.* at 602. The Eleventh Circuit affirmed, recognizing "the district court's persuasive analysis of the literature." *Hendrix*, 609 F.3d at 1199.

These principles render plaintiffs' experts' biological plausibility opinions inadmissible. Identifying the process by which ASD or ADHD occurs is still beyond the ability of medical science. Certainly, plaintiffs' experts have not done so. Drs. Pearson and Hollander do discuss the pathophysiology associated with ASD and ADHD but fall short of defining anatomical changes that cause the conditions. (*See* Pearson Rep. at 22-31; Hollander Rep. at 25-36, 53-60.) For his part, Dr. Louie could not identify "the biological mechanisms that lead to" ASD or ADHD and claimed that doing so was not part of his "assignment." (Louie Dep. 44:14-23, 50:15-23; *see id.* 45:19-46:21.)

Relatedly, none of the experts articulates a time period during pregnancy when ADHD or ASD purportedly develop, or when the fetal brain is supposedly vulnerable to the changes that they claim can cause ASD or ADHD. To the contrary, Dr. Baccarelli stated that there "may be parts of the pregnancy that are more susceptible, but the entire pregnancy is the target." (Dep. of Andrea Baccarelli 106:24-107:16, Aug. 14, 2023 (Ex. 3).) Plaintiffs' experts' admitted failure to understand—at even the most general level—when ASD or ADHD develops during pregnancy (or if the conditions develop during pregnancy at all) vividly illustrates their inability to identify the causal pathways for these conditions, rendering any opinion about how acetaminophen allegedly implicates the relevant biological mechanisms entirely speculative.

Second, plaintiffs' experts' opinions are also unreliable because they fail to justify extrapolating from findings in rodents (which were used in the majority of the mechanistic studies on which plaintiffs' experts rely) to humans. As discussed in the ASD *Daubert* Brief, extrapolation from animal studies to human beings is always "viewed with more suspicion," *Daniels-Feasel*, 2021 WL 4037820, at *13 (citation omitted), and requires "a sound basis," *Mirena I*, 169 F. Supp. 3d at 445. If animal studies are to be used, the expert must show that the

"gap between what [the animal studies] reasonably imply and more definitive scientific proof of causality is not too great." *Daniels-Feasel*, 2021 WL 4037820, at *14 (citation omitted); *see, e.g.*, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 479 (E.D. Pa. 2014) ("must establish the link between the animal mechanism and human mechanism"; excluding, inter alia, Dr. Cabrera).

No such showing had been made here. "[D]ifferent mammalian species present different physiological, biochemical and metabolic systems." *Wade-Greaux v. Whitehall Lab'ys, Inc.*, 874 F. Supp. 1441, 1453-54 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994). For instance, the affected organ in this case, the brain, is structured far differently in humans than rodents. Size is one obvious example: the human brain contains more than a thousand times more neurons than a mouse brain, and more than 400 times more neurons than a rat brain.[3] *See Daniels-Feasel*, 2021 WL 4037820, at *16 ("significant differences between animal[] and human[]"). Moreover, any neurochemical changes identified in animals are particularly difficult to link to ASD and ADHD, given the uniquely human nature of the social, behavioral, and intellectual difficulties that characterize the two disorders. *See id.* at *14, *16. As Dr. Pearson conceded at his deposition, "[a]nimals don't have ADHD or autism." (Pearson Dep. 123:7-8.)

Given these differences between species, it was incumbent on plaintiffs' experts to justify extrapolating from findings in animal studies to any conclusion about ASD or ADHD in humans. None of them have done so. Drs. Cabrera and Hollander opine generally about the utility of animal studies (which Dr. Cabrera places second from the bottom on his hierarchy of evidence) (*see* Cabrera Rep. at 13, 77-79; Hollander Rep. at 73-75), but no expert adequately explains why

[3] *See* Herculano-Houzel, *The Human Brain in Numbers: A Linearly Scaled-Up Primate Brain*, 3(31) Frontiers in Hum. Neurosci. 1 (2009). Copies of all studies cited herein are attached to the Declaration of Kristen L. Richer as Exs. 24-169.

the particular mechanistic studies on which they rely support their conclusions. This represents yet another unjustified leap of logic that renders their opinions inadmissible under *Daubert*. *See In re Zantac (Ranitidine) Prods. Liab. Litig.*, No. 20-2924, --- F. Supp. 3d ----, 2022 WL 17480906, at *165 (S.D. Fla. Dec. 6, 2022) (excluding experts in part because they did "not sufficiently explain the relevant similarities and differences" between the human and rodent stomach), *appeal dismissed*, No. 23-10090, 2023 WL 2849068 (11th Cir. Mar. 22, 2023).

Third, plaintiffs' experts' failure to distinguish between ASD and ADHD (a corollary of the fact that they have no idea how either one develops) further requires exclusion of their biological mechanism opinions. *See, e.g.*, *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) (reliance on evidence that medicine caused ischemic strokes as support for claim that it also caused hemorrhagic strokes was an improper, inadmissible "'leap of faith' supported by little more than the fact that both conditions are commonly called strokes"); *Dufour v. BP Expl. & Prod., Inc.*, No. 19-591, 2023 WL 3807923, at *11-12 (S.D. Miss. June 2, 2023) (excluding expert who "leap[ed] from data showing an increased chance of respiratory symptoms" to asthma worsening) (citing *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997)), *appeal filed*.

Here, each expert hypothesizes that acetaminophen causes "neurodevelopmental disorders," or even more vaguely "affect[s] brain development"—implicitly assuming that ASD and ADHD (as well as everything from intellectual disability to Tourette's syndrome) arise in the precisely same way. (*See, e.g.*, Pearson Rep. at 51 ("[T]he primary mechanism by which [acetaminophen] causes neurodevelopmental disorders is through oxidative stress . . . ."); Louie Rep. at 59 ("therapeutic doses of acetaminophen can affect brain development") (capitalization altered); Cabrera Rep. at 47 (acetaminophen disrupts "signaling essential for brain

development") (capitalization altered); Baccarelli Rep. at 46 ("neurodevelopmental effect on the fetal brain").) Dr. Hollander does set out separate "[h]ypotheses" for the "[p]athophysiology" of the two disorders (*see* Hollander Rep. 25-40, 53-59), but when it comes to the discussion of acetaminophen's alleged effects, he ignores any distinction (*see id.* at 78-79 ("shown to increase oxidative stress markers in the fetal brain and has been associated with adverse neurodevelopmental outcomes or deficits in animal studies"); *id.* at 83 ("responsible for behavioral and cognitive alterations").) In so doing, plaintiffs' experts do not explain why they believe ASD and ADHD (and apparently every other type of neurodevelopmental deficit or disorder) would arise from a single cause, or even from related causes.

In short, rather than come to court with demonstrated scientific pathways, plaintiffs' experts only offer "scientific guesswork." Such an approach defies the adage that "[l]aw lags behind science; it does not lead." *Mirena II* (District), 341 F. Supp. 3d at 270-71 (citation omitted). This, too, requires exclusion of their biological mechanism opinions.

II. PLAINTIFFS' EXPERTS EMPLOY UNRELIABLE METHODS IN ANALYZING SCIENTIFIC STUDIES.

Plaintiffs' experts' biological mechanism opinions are also unreliable because they apply outcome-oriented and unscientific methods in synthesizing the scientific literature. Rather than viewing the literature holistically and giving any weight or consideration to studies that undermine their hypotheses, plaintiffs' experts rely exclusively on studies with results they deem supportive—even when those results are surrounded by other (and far more numerous) negative results in the same or other studies. This approach—cherry-picking allegedly supportive data without explanation, while failing to question whether such isolated findings are spurious—reflects advocacy, not sound science, and is therefore unreliable.

First, all of plaintiffs' experts cherry-pick results that suggest acetaminophen causes

neurochemical changes that they claim are relevant to ASD and ADHD, while ignoring contrary results, in many cases from the same studies or from closely-related studies by the same authors. This slanted review of the literature is unreliable and renders their opinions inadmissible.

It is well-established that "an expert may not 'pick and choose' from the scientific landscape and present the [c]ourt with what he [or she] believes the final picture looks like." *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) ("*Rezulin I*") (citation omitted); *see, e.g.*, *Daniels-Feasel*, 2021 WL 4037820, at *5 ("An expert must not cherry-pick from the 'scientific landscape . . . .'") (citation omitted), *aff'd*, 2023 WL 4837521, at *3 (affirming exclusion because "there was sufficient support for the district court's conclusion that [expert] cherry-picked only favorable studies"); *Mirena II* (District), 341 F. Supp. 3d at 252 (excluding expert because he failed "to consider evidence that undercuts his opinion"); *In re Zantac*, 2022 WL 17480906, at *57 ("cherry-picking of data demonstrates unreliability and may justify the exclusion of an expert's testimony"). Within a study, too, an expert cannot highlight only the supportive findings while "refusing to acknowledge [the study's] deficiencies" or contrary results. *Daniels-Feasel*, 2021 WL 4037820, at *10. Of course, an expert need not credit every study or data point that has been published, but he or she must at least "acknowledge [and] account for that [contrary] evidence" and explain why he or she ultimately discounted it. *Rezulin II*, 369 F. Supp. 2d at 425.

Here, plaintiffs' experts' opinions that, e.g., "the overwhelming majority of preclinical studies investigating the effect of [acetaminophen] on neurodevelopment show that [it] causes neurodevelopmental disruption" (Pearson Rep. at 4) depend on egregious cherry-picking.[4] If a

[4] Dr. Pearson also relies heavily in his rebuttal report on Tyl, *Identification & Interpretation of Developmental Neurotoxicity Effects: A Report from the ILSI Research Foundation/Risk Science Institute Expert Working Group on Neurodevelopmental Endpoints*, 30 Neurotoxicol. Teratol. 349 (2008) ("Tyl 2008"), but this

study shows a change in a single biomarker at a single dose, plaintiffs' experts count the study as supportive of their theories. If another study shows contrary results, plaintiffs' experts ignore it. (*See, e.g.*, Pearson Rep. at 89-90 (citing Blecharz-Klin 2017[5] for the proposition that acetaminophen increased hippocampus levels of certain amino acids, but ignoring Blecharz-Klin 2014,[6] which showed no effect on the same amino acids in the same section of the brain).) And plaintiffs' experts cherry-pick positive results, while ignoring (more plentiful) negative ones even within the same study. (*See, e.g.*, Cabrera Rep. at 102 (citing Rigobello 2021[7] for the proposition that acetaminophen "decreased the levels of glutathione" even though the study showed no association between acetaminophen and glutathione in 15 of 16 tests).)

Plaintiffs' experts also claim support from any changed biomarker, regardless of the direction of the change. (*Compare* Pearson Rep. at 87 (suggesting that Blecharz-Klin 2015[8] supports a plausible mechanism in part because "P15 rats had significantly ***lower*** levels of MHPG than" controls) (emphasis added), *with id.* at 88 (suggesting that Blecharz-Klin 2016[9]

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paper does not stand for the proposition that a scientist can reach a causal conclusion based on non-replicated data. For starters, it is intended for regulators and thus works from a precautionary principle to "err on the side of caution," *id.* at 373, as Dr. Pearson admitted at his deposition (*see* Pearson Dep. 180:9-17). Moreover, all it says is that "complete concordance of effects" across "different functional domains" "is not expected and/or necessary." Tyl 2008 at 377; *see id.* at 373 (similar). That statement primarily refers to different endpoints, not to efforts to replicate the same endpoint. More importantly, it calls for careful weighing of any potentially inconsistent results, not for simply ignoring results that do not support a preferred conclusion. *See id.* at 373 ("lack of concordance . . . may induce doubt as to the toxicological or biological relevance of . . . findings" but should be considered under "a weight-of-evidence approach . . . to assess the importance to attach to the concordance, or lack thereof").

[5] Blecharz-Klin, *Paracetamol—Effect of Early Exposure on Neurotransmission, Spatial Memory & Motor Performance in Rats*, 323 Behav. Brain Res. 162 (2017) ("Blecharz-Klin 2017").

[6] Blecharz-Klin, *Paracetamol Impairs the Profile of Amino Acids in the Rat Brain*, 37 Environ. Toxicol. Pharmacol. 95 (2014).

[7] Rigobello, *Perinatal Exposure to Paracetamol: Dose & Sex-Dependent Effects in Behaviour & Brain's Oxidative Stress Markers in Progeny*, 408 Behav. Brain Res. 1 (2021) ("Rigobello 2021").

[8] Blecharz-Klin, *Effect of Prenatal & Early Life Paracetamol Exposure on the Level of Neurotransmitters in Rats—Focus on the Spinal Court*, 47 Int'l J. Dev. Neurosci. 133 (2015) ("Blecharz-Klin 2015").

[9] Blecharz-Klin, *Cerebellar Level of Neurotransmitters in Rats Exposed to Paracetamol During Development*, 68 Pharmacol. Reps. 1159 (2016).

shows a plausible mechanism in part because "the P15 group had significantly ***higher*** cerebellar concentration of noradrenaline metabolite MHPG") (emphasis added); Louie Rep. ¶¶ 162-63 (noting increase in GSH precursors to support theory of GSH exhaustion).) As noted above, Dr. Pearson goes so far as to claim that two studies, one showing that a treatment increased levels of a chemical and one showing that the same treatment decreased levels of a chemical, could be deemed consistent because both show a change. Dr. Pearson does not cite any scientific literature supporting this counterintuitive technique for manufacturing consistency.

Second, and relatedly, plaintiffs' experts place undue weight on isolated findings. Many of the mechanistic studies on which plaintiffs' experts rely tested 20 or more endpoints, the majority of which show no association with acetaminophen. *See, e.g.*, Blecharz-Klin 2015, *supra* note 8 (testing 19 different neurochemicals at two dose levels each for a total of 38 different outcomes); Blecharz-Klin 2017, *supra* note 5 (78 different total outcomes). Such studies of multiple endpoints implicate "multiplicity" problems—i.e., there is a higher likelihood that an isolated positive finding in such studies is spurious. *See, e.g.*, *Erica P. John Fund, Inc. v. Halliburton Co.*, 309 F.R.D. 251, 266 (N.D. Tex. 2015) (explaining that "use of a multiple comparison adjustment is proper . . . because of the substantial number of comparisons, thirty-five comparisons, being tested for statistical significance"). Yet, plaintiffs' experts treat any positive association in such studies as providing support for their hypotheses. And although there are established techniques to control for the probability of false positives introduced by multiple comparisons, such as requiring lower p-values to achieve statistical significance,[10] none of plaintiffs' experts employs these methodologies. (*See, e.g.*, Hollander Rep. at 79 (uncritically citing, *inter alia*, 78-outcome Blecharz-Klin study).) To the contrary, Dr. Pearson objected to

[10] Armstrong, *When to Use the Bonferroni Correction*, 34(5) Ophthalmic Physiol. Opt. 502 (2014).

the use of such a methodology in assessing the acetaminophen literature as "over-rigorous." (*See* Pearson Rep. at 102-05.) The opposite, however, is true; Dr. Pearson's approach is not rigorous enough to satisfy *Daubert*. *See In re Zoloft (Sertraline) Hydrochloride Prods. Liab. Litig.*, No. 12-2342, 2015 WL 7776911, at *5-6 (E.D. Pa. Dec. 2, 2015) (excluding expert who did not use "statistical methods for correcting for multiple comparisons within a single study"), *aff'd*, 858 F.3d 787 (3d Cir. 2017).

Taken together, plaintiffs' experts' methods essentially transform any positive finding in a rodent study of acetaminophen exposure into a possible biological mechanism. As a consequence, while there are no generally accepted mechanisms by which acetaminophen use by pregnant mothers can cause ASD or ADHD in children, plaintiffs' experts have come up with half a dozen. If such methodologies were admitted in court, experts could present to a jury hypotheses linking virtually any exposure to any purported outcome in mice or otherwise. Such a result would negate the Court's gate-keeping function. For all of these reasons, plaintiffs' experts' biological mechanism opinions should be excluded under Rule 702 and *Daubert*.

III. NONE OF PLAINTIFFS' EXPERTS' PROPOSED BIOLOGICAL MECHANISMS HAS A RELIABLE BASIS.

Plaintiffs' experts offer approximately seven hypotheses about potential biological mechanisms linking in utero acetaminophen exposure with ASD and/or ADHD, although they primarily focus on oxidative stress, endocannabinoid signaling and epigenetics. Each of these theories is unreliable for additional reasons as well.

A. The Oxidative Stress Theory Offered By Drs. Baccarelli, Cabrera, Hollander, Louie And Pearson Is Speculative.

All of plaintiffs' experts advance an oxidative stress theory, and Dr. Pearson referred to it as the "primary mechanism" on which he relies. (Pearson Rep. at 51; *see* Louie Rep. ¶¶ 104-35, 155-67; Cabrera Rep. at 35-47; Baccarelli Rep. at 45-46; Hollander Rep. at 78-79.) As explained

above, the gist of this hypothesis is that NAPQI, an acetaminophen metabolite (i.e., a substance created when the body metabolizes acetaminophen), is further metabolized by the antioxidant GSH. (*See, e.g.*, Pearson Rep. at 52.) Plaintiffs' experts posit that: (1) excessive amounts of acetaminophen, and therefore of NAPQI, can "deplete GSH levels" (*id.*; *see, e.g.*, Louie Rep. ¶ 105); (2) reduced levels of GSH either prevent the body from metabolizing further doses of NAPQI and/or leave insufficient amounts of GSH for use in "other tissues" (Hollander Rep. at 78); (3) the unmetabolized NAPQI can bind onto other macromolecules (Louie Rep. ¶ 52); (4) this supposedly increases oxidative stress, which "can cause cellular damage" in the brain (Baccarelli Rep. at 45); and (5) the cellular damage causes ASD and ADHD in a developing fetus. Plaintiffs have no reliable evidence for any of this.

First, plaintiffs' experts cherry-pick from the literature to support their theory that acetaminophen exposure at sub-toxic doses can cause oxidative stress, while downplaying or ignoring evidence to the contrary. *See, e.g.*, *Rezulin I*, 309 F. Supp. 2d at 563. For example, both Drs. Cabrera (*see* Cabrera Rep. at 102) and Pearson (*see* Pearson Rep. at 94-95) acknowledge[11] the findings in Klein 2020 that acetaminophen exposure in utero had no significant effect on GSH levels (or on LOOH, a metric of oxidative stress) after birth.[12] But neither explains why they discounted these results despite relying on the behavioral findings in the same study. (*See* Cabrera Rep. at 102; *see* Pearson Rep. at 94-95.) Drs. Hollander, Louie and Baccarelli ignore the mechanistic results of this study altogether (even as Dr. Hollander also cites the supposedly supportive behavioral results). (*See* Rebuttal Rep. of Eric Hollander at 20,

[11] Both experts phrase the issue confusingly, stating that "[r]educed glutathione . . . levels were . . . quantified" (Cabrera Rep. at 102; *see* Pearson Rep. at 94), before admitting they were actually unchanged.

[12] Klein, *Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny*, 77 Neurotoxicol. Teratol. 1 (2020) ("Klein 2020").

July 28, 2023 (Ex. 12).) Perhaps most strikingly, Dr. Louie testified that he had not even read Klein. (*See* Louie Dep. 259:10-15.) After briefly skimming the study during his deposition, he discounted it, testifying that it used an unreliable "colorimetric assay," and therefore could not replicate the results from a study by Rigobello, on which he did rely. (*Id.* 259:16-22.) Ultimately, however, Dr. Louie was compelled to admit that Rigobello and Klein used ***exactly the same*** assay, confirming his failure to properly review and assess the relevant science. (*See id.* 320:24-321:16.)

The Rigobello study is referenced not just by Dr. Louie, but by Drs. Cabrera and Pearson as well, even though none of them grapple with its predominantly negative results.[13] Dr. Cabrera suggests the study provides unequivocal support for his theory, because it showed acetaminophen "decreased the levels of glutathione (low dose, hippocampus)." (Cabrera Rep. at 102.) Dr. Louie essentially says the same, also mentioning the single positive result and ignoring the negative ones. (*See* Rebuttal Rep. of Stan Louie ("Louie Rebuttal Rep.") at 11, 15, July 28, 2023 (Ex. 21).) Dr. Pearson gets a little closer to the truth, stating that "males in the lower dose of [acetaminophen] . . . showed lower levels of reduced GSH in the hippocampus," while acknowledging that there were few "other . . . changes." (Pearson Rep. at 97.) But even this concession fails to portray the study accurately. Rigobello stratified by sex, tested at high and low concentrations of acetaminophen (as well as with a control sample), and then took GSH samples from four brain regions, for a total of 16 GSH tests. ***Fifteen of 16 tests were negative.***[14] The sole positive finding was in the male hippocampus at the lower dose. At the higher dose, the effect disappeared, and the point estimate showed, if anything, that GSH levels were higher than

[13] *See* Rigobello 2021, *supra* note 7.

[14] The study also took 48 samples for other chemical changes supposedly related to oxidative stress. Just one of those 48 was statistically significant.

in the controls, making the lower-dose results almost certainly spurious, especially since, as discussed above, Klein could not replicate them. *See, e.g.*, *Reference Manual on Scientific Evidence* (3d ed. 2011), at 603 (noting that "higher exposures should increase the incidence . . . of disease" if a relationship is truly causal).

Plaintiffs' experts also rely on studies with deep flaws and limitations that none of them acknowledge. For example, three experts do not cite any other studies of brain samples from animals exposed to acetaminophen during the rodent equivalent of gestation, while the two other experts, Drs. Cabrera and Pearson, cite Saeedan 2018,[15] in which rats were given acetaminophen injections five days after birth (which corresponds to human in utero development). (*See* Cabrera Rep. at 101-02; Pearson Rep. at 91-92.) But even this study fails to support their theory. While rats given acetaminophen during this period showed significant reductions in GSH (without correction for multiple comparisons) and significant increases in TABRs, a marker of oxidative stress, so too did rats given vaccines, including the measles-mumps-rubella and diphtheria-tetanus-pertussis vaccines, the safety of which is well-established.[16]

Plaintiffs' experts also rely on additional studies that are even less supportive of their opinions. For instance, Dr. Cabrera cites Motawi 2019,[17] a study involving adult rodent exposure, without even acknowledging that the tested rats were adults, much less explaining how the results could be extrapolated to the developing brain. (*See* Cabrera Rep. at 107). Notably, Dr. Pearson (correctly) discounted the same study, stating that because the "study used adult rats

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[15] Saeedan, *Effect of Early Natal Supplementation of Paracetamol on Attenuation of Exotoxin/Endotoxin Induced Pyrexia & Precipitation of Autistic Like Features in Albino Rats*, 26 Inflammopharmacology 951 (2018).

[16] Indeed, if this study were considered to be evidence that acetaminophen is linked to ASD or ADHD, it would also be evidence linking the vaccines to ASD—a pernicious, widely-debunked, conspiracy theory.

[17] Motawi, *Protective Effects of Betanin Against Paracetamol & Diclofenac Induced Neurotoxicity & Endocrine Disruption in Rats*, 24(7) Biomarkers 645 (2019) ("Motawi 2019").

and did not test [acetaminophen] in a developmental context, its relevance for neurodevelopmental disorders could be limited." (*See* Pearson Rep. at 70-71.)

Plaintiffs' experts also improperly rely on studies that did not involve brains at all, without offering a scientific basis to extrapolate from other organs, fluids or cells. *See, e.g.*, *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) (evidence that chemical could cause "lymphatic and hematopoietic cancers . . . not probative on the causation of brain cancer"). For example, Dr. Cabrera cites Ruepp 2002[18] for the proposition that "exposing developing brains to" acetaminophen "decreased glutathione" (Cabrera Rep. at 65), even though the study tested only adult mouse ***livers***, not brains. Similarly, Drs. Cabrera and Louie both rely on a human study (with just seven people), Jetten 2012,[19] which also looked at livers, a methodological problem that Dr. Louie brushes aside with the ipse dixit assertion that "brain tissue likely experiences similar effects as well." (Louie Rep. ¶ 160.) Dr. Louie also relies heavily on Nuttall 2003,[20] a "pilot" study that showed a 10% reduction in blood serum antioxidant capacity when adults (mostly men) took the maximum dose of acetaminophen continually for 14 consecutive days (Louie Rep. ¶¶ 126-29) and Dimova 2005,[21] a study of isolated lung cells in vitro (*id.* ¶¶ 130-32). And Dr. Hollander cites a review article, Brune 2015, which states that NAPQI "is produced in the liver and kidney cells."[22]

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[18] Ruepp, *Genomics & Proteomics Analysis of Acetaminophen Toxicity in Mouse Liver*, 65 Toxicol. Sci. 135 (2002).

[19] Jetten, *'Omics Analysis of Low Dose Acetaminophen Intake Demonstrates Novel Response Pathways in Humans*, 259 Toxicol. Appl. Pharmacol. 320 (2012).

[20] Nuttall, *The Impact of Therapeutic Doses of Paracetamol on Serum Total Antioxidant Capacity*, 28 J. Clin. Pharm. Ther. 289 (2003).

[21] Dimova, *Acetaminophen Decreases Intracellular Glutathione Levels & Modulates Cytokine Production in Human Alveolar Macrophages & Type II Pneumocytes In Vitro*, 37 Int'l J. Biochem. & Cell Bio. 1727 (2005).

[22] Brune, *Acetaminophen/Paracetamol: A History of Errors, Failures & False Decisions*, 19 Euro. J. Pain. 953 (2015).

Dr. Louie, Dr. Pearson and, in his rebuttal report, Dr. Hollander, also rely on Anand 2021,[23] a study of maternal cord blood, which reflects peripartum exposure to acetaminophen.[24] According to Dr. Louie, the study found that "as umbilical cord acetaminophen levels are increased, there is a corresponding increase in" GSH precursors (used as a proxy for GSH levels). (Louie Rep. ¶¶ 162-63.) But none of the experts acknowledges that this result (assuming for the sake of argument it is relevant) would undermine the mechanistic theory that they advance, which is that acetaminophen exposure ***depletes*** GSH.

Studies that did not use brain samples are in fact of no relevance because NAPQI forms only when unchanged acetaminophen is metabolized by cytochrome P450 enzymes such as CYP2E1, meaning, as plaintiffs' experts acknowledge, that the presence of NAPQI depends on the presence of those enzymes. (*See* Louie Dep. 182:19-23; Pearson Rep. at 9.) And P450 enzymes, such as CYP2E1, are almost absent from the brain, while abundant in the liver. Once again, Dr. Louie acknowledged the difference in CYP2E1 levels between the liver and the brain, but he failed to consider it in forming his opinions. (*See* Louie Dep. 193:14-21.)[25] In any event, even if NAPQI could form in the brain, it would be more quickly detoxified there, with less oxidative effect, because the brain has higher levels of GSH than the liver.[26]

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[23] Anand, *Perinatal Acetaminophen Exposure & Childhood Attention-Deficit/Hyperactivity Disorder (ADHD): Exploring the Role of Umbilical Cord Plasma Metabolites in Oxidative Stress Pathways*, 11(10) Brain Sci. 1302 (2021).

[24] Unlike the epidemiological study of cord blood discussed in the ASD *Daubert* Brief and the ADHD *Daubert* Brief (Ji, *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder & Autism Spectrum Disorder in Childhood*, 77(2) JAMA Psychiatry 180 (2020)), the Anand study considered only unchanged acetaminophen (not its metabolites), further limiting exposure to the hours leading up to the sample.

[25] Dr. Louie's rebuttal report states that "CYP2E1 is an inducible enzyme" that can increase tenfold in the presence of acetaminophen (Louie Rebuttal Rep. at 6-7, 9), but he admitted at his deposition that the tenfold figure is incorrect (Louie Dep. 217:5-11).

[26] *See* Raijmakers, *Glutathione S-Transferases and Thiol Concentrations in Embryonic and Early Fetal Tissues*, 16(11) Hum. Reprod. 2445 (2001).

Second, even if plaintiffs' experts had a reliable basis to opine that acetaminophen exposure could lead to GSH reduction and oxidative stress, they would have no reliable basis to link those outcomes to ASD or ADHD. In attempting to bridge this gap, plaintiffs' experts cite studies that show an association between GSH levels or oxidative stress markers and ASD or ADHD ***post-birth***. For instance, both Dr. Cabrera (*see* Cabrera Rep. at 64, 67) and Dr. Hollander (*see* Hollander Rep. at 35) cite James 2004[27] and James 2006,[28] which found higher levels of oxidative stress in post-mortem brain samples of patients with ASD. Dr. Louie cites a similar case-control study for ADHD: Nasim 2019.[29] (*See* Louie Rep. ¶ 123.) But as the Carey article points out, "retrospective studies in children already diagnosed with ASD [or ADHD] cannot provide evidence as to whether [oxidative stress] differences are a cause or a consequence" of the disorder.[30] Dr. Pearson expressly agreed with this passage (*see* Pearson Dep. 254:13-255:11; *id.* 257:25-258:6), and Dr. Louie acknowledged that "having ASD can cause [oxidative] stress," rather than the other way around (Louie Dep. 267:9-11).

As noted above, Dr. Cabrera also relies heavily on an AOP proposed by the OECD's Environmental Health & Safety Programme,[31] that purported to link proteins that can bind to

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[27] James, *Metabolic Biomarkers of Increased Oxidative Stress & Impaired Methylation Capacity in Children with Autism*, 80 Am. J. Clin. Nutr. 1611 (2004).

[28] James, *Metabolic Endophenotype & Related Genotypes Are Associated with Oxidative Stress in Children with Autism*, 141B Am. J. Med. Genet. B Neuropsychiatr. Genet. 947 (2006).

[29] Nasim, *Relationship Between Antioxidant Status & Attention Deficit Hyperactivity Disorder Among Children*, 10(41) Int'l J. Prev. Med. 1 (2019).

[30] Carey, *Examining Associations Between Prenatal Biomarkers of Oxidative Stress & ASD-Related Outcomes Using Quantile Regression*, 53(8) J. Autism Dev. Disord. 2975, 2976 (2023).

[31] Tschudi-Monnet, OECD Series on Adverse Outcome Pathways No. 20: *Binding of Electrophilic Chemicals to SH(thiol)-Group of Proteins and/or to Seleno-Proteins Involved in Protection Against Oxidative Stress During Brain Development Leading to Impairment of Learning & Memory* (2022) ("Tschudi-Monnet 2022"). The OECD is an intergovernmental group of countries, including the United States. The Environmental Health & Safety Programme is a group within the OECD that publishes research and information on chemicals and other substances to help inform regulations in member states.

"thiol (SH)- and seleno-containing proteins involved in protection against oxidative stress" (a group that includes GSH) to "impairment in learning and memory" through a long chain of causation.[32] But the AOP does not mention ADHD at all, and after criticism from reviewers who noted that "learning and memory" impairment are very different from ASD, the author agreed to "totally remove the autism aspect and consider only learning and memory impairment, for which there is enough experimental support."[33] This further renders Dr. Cabrera's opinion unreliable. *See, e.g.*, *Daniels-Feasel*, 2021 WL 4037820, at *4, *10 (noting that an expert "must not exceed the limitations the authors themselves place on [a] study" and excluding expert because he "press[ed] conclusions that the . . . authors were not willing to make") (citation omitted).

In short, plaintiffs' experts' primary biological theory depends on two leaps in logic, ignores contrary evidence and stretches cherry-picked evidence well beyond the conclusions that the literature actually supports. These are the hallmarks of unreliable expert opinions.

B. The Endocannabinoid Theory Offered By Drs. Baccarelli, Cabrera, Hollander And Pearson Is Unreliable.

Drs. Pearson, Cabrera and Hollander, and very briefly, Dr. Baccarelli, also suggest that acetaminophen can somehow interfere with the endocannabinoid system. (*See* Pearson Rep. at 61-63; Cabrera Rep. at 47-52; Baccarelli Rep. at 46-47; Hollander Rep at 79-81.) According to this theory, an extremely minor acetaminophen metabolite (AM404) binds to the primary cannabinoid receptor CB1, preventing reuptake of other chemicals and leading, at least temporarily, to higher free levels of the endocannabinoid anandamide. Dr. Hollander, but no other plaintiffs' expert, suggests that the body may adjust by permanently lowering anandamide

[32] Tschudi-Monnet 2022, *supra* note 31, at 11, 32.

[33] Internal Review Charge Questions, at 14 (Apr. 13, 2018), https://aopwiki.org/system/dragonfly/production/2018/06/22/zeas7ec1l_Questions_to_reviewers_Compiled_Comments_IR_charge_questions_AOP17.docx.

levels. (Hollander Rep. at 80.) Based on little more than a general view that the endocannabinoid system is important for brain development and that disrupting it is therefore undesirable, plaintiffs' experts posit that AM404 binding must lead to the development of ASD or ADHD. Once again, they do not explain how or why that would occur.[34]

This theory is just as speculative as the first. To begin, plaintiffs' experts have no real evidence that acetaminophen prevents reuptake or increases free levels of endocannabinoids. In support of that hypothesis, the experts cite a handful of review articles that in turn rely almost entirely on original animal research,[35] meaning that the very first step in their theory should be "viewed with . . . suspicion." *Daniels-Feasel*, 2021 WL 4037820, at *13 (citation omitted). In addition, plaintiffs' experts offer nothing but speculation and strained analogy to support the hypothesis that endocannabinoid dysregulation in utero causes ASD or ADHD. *See, e.g.*, *Rezulin II*, 369 F. Supp. 2d at 426. A review of the literature on which they rely makes the point. For example, Drs. Hollander (Hollander Rep. at 80) and Cabrera (Cabrera Rep. at 57) cite an article by Schultz 2012,[36] which found that soaking mouse neurons in an acetaminophen metabolite solution (but not an acetaminophen solution) induced cell death, and that a solution of anandamide (an endocannabinoid) did the same. But neither of them tries to explain how in vitro cell death in mice relates to ASD or ADHD or how the fact that both an acetaminophen metabolite and an endocannabinoid neurotransmitter had similar in vitro effects in mice would

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[34] This theory is contrary to scientific consensus insofar as increased endocannabinoids have been proposed as a ***treatment*** for ASD. Chakrabarti, *Endocannabinoid Signaling in Autism*, 12 Neurotherapeutics 837 (2015).

[35] For instance, Dr. Cabrera cites Bertolini, *Paracetamol: New Vistas of an Old Drug*, 12 CNS Drug Rev. 250 (2006), which in turn cites two animal studies, while Dr. Baccarelli cites Angelis, *Part I. Mechanisms of Actions & Metabolism of Acetaminophen Related to the Neonatal Brain*, 159 Early Hum. Dev. 1 (2021), which in turn cites three animal studies for the proposition that "[a]cetaminophen exerts a well[-]described action on cannabinoid receptors."

[36] Schultz, *Effects of the Analgesic Acetaminophen (Paracetamol) & its para-Aminophenol Metabolite on Viability of Mouse-Cultured Cortical Neurons*, 110 Basic Clin. Pharmacol. Toxicol. 141 (2012).

show that the in vivo effects of acetaminophen are mediated through the endocannabinoid system in humans.

Drs. Cabrera and Pearson each filed a supplemental report to address a forthcoming article that they believe supports their theories: Klein 2023.[37] But their discussions of this study only underscore their biased approach to the literature because they present the study as clearly supportive of their position, with a one-sided and misleading summary of what it says. (*See* Suppl. Rep. of Brandon Pearson ("Pearson Suppl. Rep.") at 3, July 14, 2023 (Ex. 22) (endocannabinoid agonist (i.e., a chemical that promotes a cellular response in the endocannabinoid system) "mediated some, but not all, of [acetaminophen's] . . . effects"); Suppl. Rep. of Robert Cabrera ("Cabrera Suppl. Rep.") at 2-3, July 17, 2023 (Ex. 23) ("identified a significant interaction" between acetaminophen and agonist).) In fact, however, the study showed that for the vast majority of behavioral tests, use of an endocannabinoid agonist did ***not*** alter the effect of acetaminophen, suggesting that in utero acetaminophen exposure does not significantly affect the endocannabinoid system. And where the acetaminophen/agonist cocktail did alter behavior, it did so in a way that cuts against plaintiffs' experts' theories. For instance, both experts obliquely acknowledge that agonist treatment ***reversed*** the supposed effect of acetaminophen on nest-seeking behavior, a rodent behavior ostensibly related to either ASD or ADHD. (*See* Pearson Suppl. Rep. at 3; Cabrera Suppl. Rep. at 2-3.) But if any effects of acetaminophen were mediated through the endocannabinoid system, the result would have been the reverse: an agonist would have increased the neurodevelopmental effects of acetaminophen.

Dr. Baccarelli attempts to connect the endocannabinoid theory to the development of

[37] Klein, *Gestational Paracetamol Exposure Induces Core Behaviors of Neurodevelopmental Disorders in Infant Rats & Modifies Response to a Cannabinoid Agonist in Females*, 99 Neurotoxicol. Teratol. 1 (2023).

ASD by noting that "[a]lterations of the endocannabinoid system have been found in both the brain and the immune system of humans with ASD." (Baccarelli Rep. at 46.) Likewise, Dr. Pearson reports that endocannabinoid dysfunction "has been specifically linked to ASD" and that "[e]ndocannabinoid metabolism has been shown to be disrupted in childhood ADHD." (Pearson Rep. at 62.) But as discussed above with respect to oxidative stress, the fact that a biomarker is altered in individuals with ASD or ADHD only begs the question of causation, since "alterations of the endocannabinoid system" are just as likely to result from ASD or ADHD as to cause it.

Finally, most of plaintiffs' experts analogize AM404 to cannabis (Baccarelli Rep. at 47; Cabrera Rep. at 51; Pearson Rep. at 62), claiming that both drugs affect the endocannabinoid system, that some studies have associated prenatal marijuana exposure with an increased risk of ASD or ADHD, and that the same risk must therefore apply to acetaminophen. In fact, much of the literature plaintiffs cite does ***not*** suggest that marijuana increases ASD or ADHD risk.[38] But even if the experts could support that premise, reasoning by analogy to another class of drugs that supposedly acts on similar regions of the body is, at best, the statement of a mere hypothesis, which is not admissible under *Daubert*. *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005); *Mirena II* (District), 341 F. Supp. 3d at 289.

C. <u>The Epigenetic Theories Offered By Drs. Baccarelli, Hollander, Louie And Pearson Are Unreliable.</u>

Plaintiffs' experts next hypothesize that acetaminophen leads to epigenetic changes, primarily through DNA methylation (which occurs when a methyl group is added to a DNA

[38] *See, e.g.*, DiGuiseppi, *Peri-Pregnancy Cannabis Use & Autism Spectrum Disorder in the Offspring: Findings from the Study to Explore Early Development*, 52 J. Autism Dev. Disord. 5064, 5064 (2022) ("Adjusted odds of peri-pregnancy cannabis use did not differ significantly between ASD cases and . . . controls."); Nutor, *Prenatal Cannabis Use & Offspring Autism-Related Behaviors: Examining Maternal Stress as a Moderator in a Black American Cohort*, J. Autism Dev. Disord. 1, 10 (2023) ("We found no evidence that prenatal cannabis exposure increases risk for ASD-related behaviors . . . .") (both cited in Cabrera Rep. at 51 n.174).

molecule without changing the coding), resulting in neurodevelopmental disorders. This theory, too, is highly speculative.

First, plaintiffs' experts once again rely on cherry-picked literature. In particular, Drs. Louie (*see* Louie Rep. ¶¶ 176-79), Baccarelli (*see* Baccarelli Rep. at 50), and Hollander (*see* Hollander Rep. at 85),[39] rely heavily on Gervin 2017, which showed different patterns of DNA methylation in the umbilical cord blood of children who were ultimately diagnosed with ADHD and who had been exposed to acetaminophen in utero than in controls.[40] But none of these experts acknowledged in his opening report that the same research group later revisited their initial study using a larger sample from the same cohort and "improved" methods, and obtained the opposite results (Olstad 2023).[41] *See, e.g.*, *Rezulin II*, 369 F. Supp. 2d at 425.

Plaintiffs' experts also reference a few additional experimental studies, but those studies do not support their opinions either. Drs. Hollander (*see* Hollander Rep. at 85-86) and Baccarelli (*see* Baccarelli Rep. at 50) cite Spildrejorde,[42] an in vitro study performed on a cell line derived from a single embryo. That study reported that cells, when constantly soaked in acetaminophen, showed patterns of methylation, as well as chromatin opening, another form of gene expression, that were different from controls. It also noted that some of the differentially regulated genes

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[39] Dr. Pearson also touches on epigenetic changes, but makes no real effort to link the concept to either acetaminophen or ASD and ADHD.

[40] Gervin, *Long-Term Prenatal Exposure to Paracetamol is Associated with DNA Methylation Differences in Children Diagnosed with ADHD*, 9(77) Clin. Epigenetics 1 (2017) ("Gervin 2017").

[41] Olstad, *No Impact of Prenatal Paracetamol & Folic Acid Exposure on Cord Blood DNA Methylation in Children with Attention-Deficit/Hyperactivity Disorder*, 14 Frontiers in Genetics 1 (2023). Although this paper was published only about a week before plaintiffs' expert reports were submitted, it is hard to believe the experts were simply unaware of it since some of them were able to locate a yet-unreviewed and yet-unpublished report by similar authors that they thought supported their position. *See* Spildrejorde, *Multi-Omics Approach Reveals Dysregulated Genes During HESCs Neuronal Differentiation Exposure to Paracetamol*, preprint at https://www.biorxiv.org/content/10.1101/2022.12.08.519620v2.full.pdf ("Spildrejorde 2023").

[42] Spildrejorde 2023, *supra* note 41.

overlapped with genes identified in the Gervin study. But these in vitro findings are worlds away from the reality of animal exposure, much less human exposure, which is why the authors acknowledged that their findings "need to be validated by in vivo models and targeted human" studies.[43]

Second, plaintiffs' experts have no evidence that epigenetic changes (even if they occur) could lead to the development of ASD or ADHD. Epigenetic expression, and occasional changes in that expression, are ordinary features of healthy cell biology—and epigenetic expression is constantly altered through aging or everyday activities like exercise or diet. Thus, it is not remotely self-evident that an exposure that causes epigenetic changes would have a deleterious effect of any sort—much less that those changes would cause ASD or ADHD.

The few studies on which plaintiffs' experts rely do not suggest otherwise. All of plaintiffs' experts except Dr. Pearson cite Eslamimehr 2022[44] and/or Addo 2019,[45] two epidemiological studies suggesting that minor changes occur in methylation patterns among the children of mothers who used acetaminophen during pregnancy. Neither suggested, even theoretically, however, that the few methylation sites identified were related to ASD, ADHD or any other neurodevelopmental disorder.[46] In addition, the same experts point to Carter & Blizard 2016,[47] a study in which the authors queried a database to see how many of 206 genes

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43 *Id.* at 30.

44 Eslamimehr, *Association of Prenatal Acetaminophen Use & Acetaminophen Metabolites with DNA Methylation of Newborns: Analysis of Two Consecutive Generations of the Isle of Wright Birth Cohort*, 8(1) Environ. Epigenetics 1 (2022) ("Eslamimehr 2022").

45 Addo, *Acetaminophen Use During Pregnancy & DNA Methylation in the Placenta of Extremely Low Gestational Age Newborn (ELGAN) Cohort*, 5(2) Environ. Epigenetics 1 (2019).

46 *See* Eslamimehr 2022, *supra* note 44 (genes potentially related to respiratory disorders and diabetes, but clinical significance unknown).

47 Carter & Blizard, *Autism Genes Are Selectively Targeted by Environmental Pollutants Including Pesticides, Heavy Metals, Bisphenol A, Phthalates & Many Others in Food, Cosmetics or Household Products*, 101 Neurochem. Int'l 83 (2016).

purportedly involved in ASD had ever reported an interaction with a series of environmental compounds including acetaminophen. (*See* Louie Rep. ¶¶ 181-84; Hollander Rep. at 83-84; Baccarelli Rep. at 49; Cabrera Rep. at 176-77.) Because the database included any reported interaction, regardless of type of study, or nature of the observed effect, the results say more about how often a compound had been the subject of research than anything else.

In any event, none of the studies, including those that purported to relate to genes relevant to ASD or ADHD, tested cells in the brain. That fact is important because epigenetic changes are not consistent across the body.[48] Thus, tests performed on umbilical cord blood, as in Gervin or Eslamimehr, or in the placenta, as in Addo, would not necessarily reflect brain gene expression. Indeed, the Gervin study on which plaintiffs' experts principally rely expressly cautions that "whether these differences [in cord blood DNA] also reflect changes in the brain ***needs to be established***."[49] Because plaintiffs' experts failed to heed that warning, their opinions are unreliable. *See, e.g.*, *Daniels-Feasel*, 2021 WL 4037820, at *4, *10.[50]

In short, even if acetaminophen causes epigenetic changes in umbilical cord blood or the placenta, plaintiffs' experts have no idea whether such changes are harmful at all, much less whether they also occur in the brain or specifically cause ASD or ADHD. Thus, as with their oxidative stress theory, plaintiffs' experts lack the evidence they would need to offer a reliable opinion on this theory. *Rezulin II*, 369 F. Supp. 2d at 426.

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[48] Jambhekar, *Roles and Regulation of Histone Methylation in Animal Development*, 20(10) Nat. Rev. Mol. Cell Biol. 625 (2019).

[49] Gervin 2017, *supra* note 40, at 5 (emphasis added).

[50] With very little explanation, Drs. Pearson and Cabrera also posit that acetaminophen can damage DNA itself in a way that could cause some sort of neurodevelopmental disorder. (*See* Pearson Rep. at 57-58; Cabrera Rep. at 45-46.) In particular, citing to Bender 2004, they suggest that NAPQI damages DNA molecules by modifying the effect of topoisomerase II, an enzyme that helps cut and detangle DNA. To the extent either expert seriously advances this as a plausible mechanism, the "analytical gap" between the Bender study—which showed certain molecular interactions in vitro and not even within a cell—and any clinical effect is obviously far too large, *Joiner*, 522 U.S. at 146, rendering such opinions highly speculative.

D. Plaintiffs' Experts' Remaining Theories Suffer From The Same Flaws.

Plaintiffs' experts also offer a handful of other speculative hypotheses related to levels of non-endocannabinoid neurotransmitters, BDNF levels, cell death, and prostaglandin disruption. None of these theories comes anywhere close to showing biological plausibility.

First, each of these theories is, again, derived from cherry-picked studies and results. For instance, Dr. Pearson claims that acetaminophen "may affect normal serotonergic signaling" (Pearson Rep. at 64), citing Blecharz-Klin 2017.[51] That study involved rats that were given acetaminophen well after birth, at an age equivalent to human toddlers, and showed elevated levels of dopamine and dopamine metabolites in one brain region, and of a serotonin metabolite in another. But Blecharz-Klin tested so many end points—78 different neurotransmitters or metabolites (13 chemicals, 2 dosage levels, 3 brain sites)—that some positive associations were likely by chance alone. And other studies, including one by the same research group, have reported either no change or decreases in dopamine and serotonin levels following acetaminophen treatment.[52]

The theory that acetaminophen alters levels of BDNF, advanced by Drs. Pearson, Hollander, Louie and Baccarelli, is based on a similarly selective culling of the evidence. For this theory, the experts primarily rely on Viberg 2014,[53] which found increased levels of BDNF

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[51] Blecharz-Klin 2017, *supra* note 5.

[52] *See, e.g.*, Motawi 2019, *supra* note 17 (decreased dopamine); Vigo, *Acute Acetaminophen Intoxication Induces Direct Neurotoxicity in Rats Manifested as Astrogliosis & Decreased Dopaminergic Markers in Brain Areas Associated with Locomotor Regulation*, 170 Biochem. Pharmacol. 1 (2019) (decreased dopamine); Blecharz-Klin 2015, *supra* note 8 (decreased dopamine levels, increased serotonin levels); Blecharz-Klin, *Hypothalamus—Response to Early Paracetamol Exposure in Male Rats Offspring*, 76 Int'l J. Dev. Neurosci. 1 (2019) (unchanged serotonin). In like manner, Pearson mentions a study suggesting changes in a certain neurotransmitter level, while ignoring a study from the same research group showing no change.

[53] *See* Viberg, *Paracetamol (Acetaminophen) Administration During Neonatal Brain Development Affects Cognitive Function & Alters Its Analgesic & Anxiolytic Response in Adult Male Mice*, 138(1) Toxicol. Sci. 139 (2014) ("Viberg 2014").

in the prefrontal cortex, and decreased levels in the parietal cortex, of ten-day-old rodents treated with acetaminophen. (*See* Pearson Rep. at 100-01; Louie Rep. ¶ 151; Hollander Rep. at 82; Baccarelli Rep. at 47.) But none of the experts attempts to harmonize that finding with other studies (that they cite for other propositions) showing no similar changes in those brain regions.[54]

Finally, Dr. Pearson and (to a lesser extent) Drs. Cabrera and Louie suggest that acetaminophen or its metabolite NAPQI is directly cytotoxic, leading to programmed cell death, also known as apoptosis. (*See* Pearson Rep. at 58; Cabrera Rep. at 47, 62-63, 66; Louie Rep. ¶ 106.) The primary support any of them offers for the idea that acetaminophen can increase apoptosis comes from Posadas 2010[55] (cited in Pearson Rep. at 58-59, 70, 118-19; Cabrera Rep. at 46, 47, 66, 105; Louie Rep. ¶¶ 106, 154). That study, which was performed on both adult rats and on adult rat cells in vitro, used acutely toxic doses of acetaminophen. Its results are therefore both unsurprising and irrelevant to what happens at a therapeutic dose. Dr. Pearson acknowledged as much, noting that human acetaminophen blood concentrations of 165-992 μM are "toxic" (Pearson Rep. at 13), whereas the concentration in the Posadas study was far greater, at 1-2 mM (*id.* at 70). Dr. Louie avoided this conclusion only by making an elementary math error, stating that "acetaminophen can cause concentration-dependent neuronal death in vitro at concentrations (1 and 2 mM), well below the steady-state concentrations observed in humans, which ranges from 66 to 198 micromolar (μM)." (Louie Rep. ¶ 154.) But there are 1,000 micromoles (μM) in a millimole (mM); thus, as he had to admit at his deposition, the acetaminophen concentrations in Posadas et al. 2010 were actually five to 30 times greater than

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[54] *See* Klein 2020, *supra* note 12 (cited in Pearson Rep. at 94-95); Blecharz-Klin 2017, *supra* note 5 (cited in Hollander Rep. at 79; Pearson Rep. at 89-90) (both showing no changes in prefrontal cortex).

[55] Posadas, *Acetaminophen Induces Apoptosis in Rat Cortical Neurons*, 5(12) PLoS ONE 1 (2010).

those in humans.[56] (Louie Dep. 228:2-8.)

Second, plaintiffs' experts have zero evidence that any of these supposed neurochemical changes causes ASD or ADHD. For instance, Dr. Pearson claims that "studies have highlighted alterations in serotonin level[] receptors in autistic people" (Pearson Rep. at 64-65), but he does not explain whether higher or lower levels of serotonin are associated with the disorder, and the cited literature is woefully inconsistent.[57] Moreover, even if he could articulate consistent associations, that would not show whether serotonin levels cause ASD or ADHD or whether the conditions affect serotonin levels (the "chicken and egg" problem). Likewise, none of plaintiffs' experts articulates whether increased BDNF levels or decreased BDNF levels would lead to the development of ASD or ADHD (the primary study on which they rely shows increased levels in some areas, and decreased levels in others).[58] For instance, Dr. Baccarelli states that "[d]isruption of BDNF . . . has been observed in patients" with neurodevelopmental disorders (Baccarelli Rep. at 47), but does not further explain the supposed association. And, as with Dr. Pearson's neurotransmitter theory, Dr. Baccarelli offers no basis to conclude that BDNF "disruption" contributes to the development of either ASD or ADHD (as opposed to the reverse).

Plaintiffs' experts' apoptosis theory falters for similar reasons—they cannot connect it to any clinically relevant outcome, much less make it "all the way down the[] causal chain" to ASD or ADHD. *Rezulin II*, 369 F. Supp. 2d at 426. Without citing any science, Dr. Pearson asserts

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[56] Plaintiffs' experts' remaining theory—that acetaminophen can cause ASD or ADHD through the inhibition of prostaglandins—is the only one that makes it past the first step. Acetaminophen almost certainly does inhibit prostaglandin synthesis, since that is how pain relievers work, but the experts have no explanation as to how or why that would lead to ASD or ADHD.

[57] Dr. Pearson cites one study that says "***[r]eduction*** in serotonergic function has been linked" to one subtype of ASD, Kessi, *Attention-Deficit/Hyperactivity Disorder Updates*, Frontiers in Mol. Neurosci. (2022) (emphasis added), and another that says ASD is associated with ***higher*** serotonin levels, Marotta, *The Neurochemistry of Autism*, 10(3) Brain Sci. 1 (2020).

[58] *See* Viberg 2014, *supra* note 53.

that "excessive apoptosis . . . can impair various cognitive, sensory, and motor processes." (Pearson Rep. at 58.) This is pure ipse dixit, but even taken at face value, Dr. Pearson does not explain why such impairments would lead to ASD and/or ADHD, specifically.

Finally, plaintiffs' experts hypothesize that "[p]rostaglandin E2 is involved in the normal development of the brain" (Baccarelli Rep. at 46), and that acetaminophen could somehow impair this process and thereby cause ASD or ADHD. As noted above, acetaminophen almost certainly does inhibit prostaglandin synthesis in order to achieve its analgesic and antipyretic effects. Indeed, almost all over-the-counter analgesics and antipyretics, including NSAIDs such as ibuprofen and aspirin, do the same, because prostaglandins (particularly prostaglandin E2) mediate pain, fever and inflammation. But any link between that fact and ASD or ADHD is pure speculation.

Dr. Pearson rests his opinion on a single study of 12 rats, in which acetaminophen was used as a control: Dean 2012.[59] In that study (which has never been replicated in other animals, let alone observed in humans), acetaminophen increased spinophilin levels.[60] Dr. Pearson opines that spinophilin is "associated with dendritic synaptic spines" (Pearson Rep. at 85), but neither Dr. Pearson nor any other expert attempts to explain why that would be relevant to ASD or ADHD.[61] Dr. Baccarelli leans heavily on the fact that other "chemicals that disrupt the levels of prostaglandin E2 . . . are . . . linked to ASD" (Baccarelli Rep. at 46), but this argument proves too

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[59] Dean, *Prostaglandin E2 is an Endogenous Modulator of Cerebellar Development & Complex Behavior During a Sensitive Postnatal Period*, 35(8) Euro. J. Neurosci. 1218 (2012).

[60] Dr. Cabrera refers to results that were shown with other medications in his report relating to, among other things, brain atrophy and behavior, but those end points were not reported for acetaminophen. (*See* Cabrera Rep. at 99-100.)

[61] Elsewhere in his report, Dr. Pearson cites a study that supposedly showed acetaminophen "reduced" "dendritic spines," leading to cognitive impairment. (*See* Pearson Rep. at 20.) This is yet another example of his results-oriented approach, wherein he will treat any observed change, in any direction, as evidence of neurotoxicity, which he then links to ASD and ADHD.

much. Other analgesic medications "disrupt the levels of prostaglandin E2" in a manner far more analogous to acetaminophen than the examples Dr. Baccarelli offers, but they have never been suggested to increase the risk of ASD or ADHD. Dr. Baccarelli does not address this glaring problem with his hypothesis. *See, e.g.*, *Mirena II* (District), 341 F. Supp. 3d at 252 (excluding expert who considered analogy to one type of contraceptive but not to a more closely-related type). Finally, Dr. Hollander cites a review article that posits that increased levels of "COX-derived lipid mediators such as" prostaglandin E2 following infection might increase the risk of ASD,[62] but if that were true, it would suggest that COX-inhibitors like acetaminophen have a ***protective*** effect with respect to ASD, the opposite of causation.

In short, all of plaintiffs' experts' mechanistic theories pile speculation on speculation. Accordingly, they should all be excluded from trial.

CONCLUSION

For the foregoing reasons, all of plaintiffs' experts' opinions on proposed biological mechanisms are unreliable, and they should all be excluded.

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Respectfully submitted,

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[62] Tamiji & Crawford, *The Neurobiology of Lipid Metabolism in Autism Spectrum Disorders*, 18 Neurosignals 98 (2010). Dr. Hollander claims that this article shows that "disruption in signaling of the prostaglandin E2 pathway . . . can lead to neurodevelopmental disorders" (Hollander Rep. at 79), again ignoring the direction of the disruption.

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